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Disseminated histoplasmosis in an AIDS patient treated with itraconazole

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Abstract

A patient with AIDS presented with a fever, shortness of breath and a productive cough. A provisional diagnosis of Pneumocystis carinii pneumonia was made; however, blood cultures and bone marrow examination revealed disseminated infection with *Histoplasmosis capsulatum*. This was treated by itraconazole with initial success, but the patient relapsed while on maintenance therapy.

Introduction

Disseminated histoplasmosis is an unusual dimorphic fungal opportunistic infection which usually occurs in endemic areas such as southern North America, South America, tropical Africa or the Far East. Initial infection usually results from inhalation of infected spores and if not controlled by cell-mediated immunity, can lead to disseminated disease by haematogenous spread.[1] Histoplasmosis may also develop by reactivation, as well as primary infection, in immuno-compromised patients and can recur years after a patient has left an endemic area.[2] We report a case in which the presentation mimicked a common opportunistic infection and describe its treatment with oral itraconazole.

Case report

A 31 year old heterosexual man, who was first diagnosed as being infected by human immunodeficiency virus (HIV) in January 1987, presented with lethargy, fever, cough productive of clear sputum and shortness of breath for 4 days, associated with left-sided chest pain.

A diagnosis of AIDS had been made in October 1989 on the basis of concurrent opportunistic infections with *Pneumocystis carinii pneumonia* (PCP) and oesophageal candidosis. Subsequently he had two further confirmed episodes of PCP and frequently recurrent genital *herpes simplex* virus (HSV) infections. On admission he was receiving zidovudine 100 mg qds, ketoconazole 200 mg bd, acyclovir 400 mg bd and dapsone 100 mg mane. The patient had retired from overseas military service on the grounds of ill health. He gave a history of numerous sexual partners whilst in Africa and French Guyana, which was presumed to be his major risk factor for HIV infection.

On examination he was found to be pyrexial (40°C), cyanosed with clubbing of his fingers and dyspnoeic at rest. Basic investigations on admission revealed a pancytopaenia (Hb 10·3 g/dl, WBC $1{\cdot}1 \times 10^9$/l, platelets 18/mm^3), arterial hypoxia (pO_2 9 kpa, pCO_2 3·5 kpa), normal serum electrolytes, urea, creatinine, and a CD4 lymphocyte count of 8/mm^3. A chest radiograph revealed mild bilateral interstitial shadowing.

A provisional diagnosis of PCP was made and intravenous pentamidine therapy was commenced (trimethoprim-sulphamethoxazole was felt to be contraindicated owing to the pancytopaenia). Samples were obtained by sputum induction and bronchoscopy for microscopy; however, these failed to confirm PCP. He remained pyrexial, but his pO_2 improved to 10·2 kpa. Yeast-like organisms were seen on direct microscopy of the centrifuged blood culture samples (fig 1). A bone marrow aspirate and trephine revealed histoplasmosis laden macrophages and general reticulo-endothelial dysplasia (fig 2). Culture of the bone marrow and blood cultures confirmed disseminated *H capsulatum* infection.

Therapy with itraconazole 400 mg mane was commenced, as amphotericin was felt to be contraindicated because of the potential risk of renal toxicity when combined with pentamidine.

Indeed, after seven days, inhaled nebulised pentamidine had to be substituted for intravenous therapy because of deteriorating renal function, which then recovered completely. He was discharged after 18 days having made a full clinical recovery, with a normal pO_2, a resolving appearance on the chest radiograph, and he was afebrile. Maintenance therapy with itraconazole (400 mg/day) was pre-

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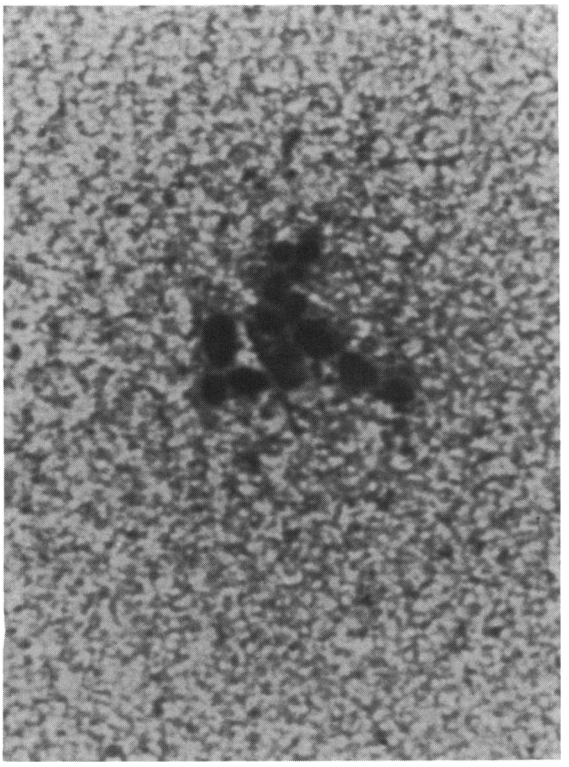

Figure 1 Cluster of histoplasma spores in spun blood culture. Gram stain (× 1000).

scribed. A repeat bone marrow examination after six weeks showed no histological evidence of histoplasmosis and cultures failed to grow yeasts.

However, four months later the patient was readmitted complaining of fevers, lethargy and shortness of breath. The initial investigations again revealed profound pancytopaenia (Hb 4·6 g/dl, WCC $0{\cdot}8 \times 10^9$/l, platelets 14/mm^3), bone marrow aspiration showed a heavy infestation of *H capsulatum* and a chest radiograph showed pulmonary oedema and areas of consolidation. He was treated with amphotericin i.v. (50 mg/day), triple antibiotic therapy and blood transfusion. He made a rapid clinical improvement. The *H capsulatum* isolated during this admission was found to be sensitive to itraconazole, ketoconazole and amphotericin in the yeast phase but resistant to amphotericin in the mycelial phase.

Discussion

In this case the isolation of *H capsulatum* suggests that this infection was acquired on the American continent rather than in Africa where *H dubosi* is more prevalent.[3]

Amphotericin has previously been accepted as the treatment of choice for disseminated histoplasmosis;[1] however, it has several disadvantages which include the necessity of intravenous administration, common side effects of fever, chills, headache and myalgia as well as significant toxicity to bone marrow and kidneys.[4] Although ketoconazole has been shown to be an effective treatment for histoplasmosis when given for longer than six months,[5] it is possible that the initial reactivation occurred in this case because of intermittent usage and the reduced bioavailability in AIDS patients due to gastric hypochlorhydria.[6] Similarly we have observed decreased itraconazole absorption in AIDS patients compared with seronegative controls (unpublished data).

The experience with itraconazole as sole therapy for histoplasmosis is limited.[1 7] One American series claimed a similar response rate to that of amphotericin, with minimal toxicity.[1] In our patient, during the initial admission, oral itraconazole at a dose of 400 mg/day resulted in clinical, histological and mycological cure after one month's treatment, with no toxicity. As with other opportunistic infections in AIDS patients, relapses may occur despite maintenance therapy.[8] As the organism was sensitive to itraconazole the likely reasons for this relapse are an insufficient systemic concentration due to poor compliance or reduced drug absorption.

In summary this case demonstrates that clinicians in non-endemic areas for *H capsulatum* infection should be aware of this unusual opportunistic pathogen in patients with AIDS, especially as it may masquerade as a far more common illness.

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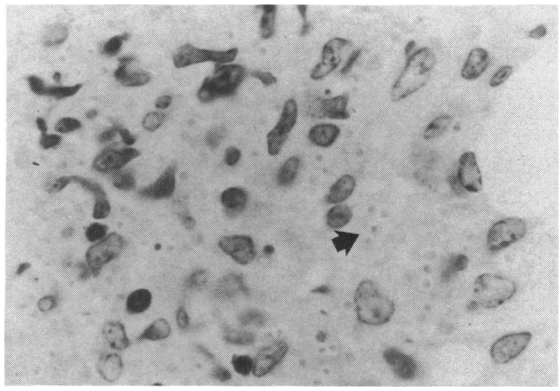

Figure 2 Bone trephine showing histoplasmosis laden macrophages (arrow). H and E (× 500).

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